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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,893	MCCORMICK ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-50 and 54-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-50 and 54-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/8/02; 7/26/02;* 3/8/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The preliminary amendment filed 2/8/2002 has been entered in full.

2. Claims 1-40 and 51-53 have been canceled.

   Claims 41-44 have been amended.

   Claims 54-57 have been added.

3. Claims 41-50 and 54-57 are pending and under examination.

Specification

4. The disclosure is objected to because of the following informalities:

The first line of the specification needs to be updated with a priority statement indicating that the instant application is a divisional of USSN 09/522,900, filed 3/10/2000, which claims benefit to U.S. provisional application 60/155,979, filed 9/24/1999. For additional information on claiming benefit to an earlier filed application see United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 41-50 and 54-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 41-50 and 54-57 are indefinite for reciting "derived" in claim 1. The term "derived" is not one, which has a universally accepted meaning in the art nor is it one, which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of an ascertainable meaning for said phrase. Since it is unclear how the nucleic acid encoding the polypeptide self-antigen are to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of molecules to said phrase. In addition, since the term "derived" does not appear to be clearly defined in the specification, and the term can encompass nucleic acids with nucleotide substitutions, insertions, or deletions, chemically derivatized molecules, or even mimetics. In the absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

b. Claim 41-50 and 54-57 are indefinite for reciting "encoded at least in part" in claim 41. Does the nucleic acid encode only a part of the polypeptide self-antigen or is the entire polypeptide self-antigen encoded by the nucleic acid? Further, if only part of the polypeptide self-antigen is encoded by a nucleic acid, what part or parts of the polypeptide self-antigen is/are encoded by the nucleic acid?

c. Claim 41-50 and 54-57 are indefinite for reciting "at risk of developing a tumor, encoded at least in part by a nucleic acid in the cells of said tumor" in claim 41. It is unclear what is contemplated by the phrase "at risk of developing a tumor, encoded at least in part by a nucleic acid in the cells of said tumor" because a subject that is at risk of developing a tumor has not actually developed a tumor and thus, it is unclear if the polypeptide self-antigen (i.e., tumor-specific antigen) is actually encoded in the cells of a subject at risk of developing a tumor. Is the polypeptide self-antigen encoded only in the tumor cells (i.e., unique to tumor cells) of a subject or is the polypeptide self-antigen also expressed in normal cells of a subject at risk of developing a tumor?

d. Claim 48 recites the limitation "the polypeptide". There is insufficient antecedent basis for this limitation in the claim. Does the phrase "the polypeptide" mean the polypeptide self-antigen or some other polypeptide?

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 41-50 and 54-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing a tumor-specific immune antibody response in a subject who has or had a B cell lymphoma comprising administering to a subject with a B cell lymphoma a B-cell

lymphoma surface immunoglobulin antigen (i.e., idiotype), wherein the B-cell lymphoma surface immunoglobulin antigen is expressed in a cell or organism as a scFv, does not reasonably provide enablement for (a) a method of inducing a tumor-specific immune antibody response in a subject who has or had just any tumor comprising administering a vaccine composition comprising a B-cell lymphoma surface immunoglobulin antigen expressed in a cell or organism as a scFv; (b) a method of inducing a tumor-specific immune antibody response in a subject who has or had a B cell lymphoma comprising administering a vaccine composition comprising just any polypeptide self-antigen; (c) a method of inducing a tumor-specific immune antibody response in a subject who has or had just any tumor comprising administering a vaccine composition comprising just any polypeptide self-antigen; (d) a method of inducing a tumor-specific immune antibody response in a subject who has or had just any tumor comprising administering a vaccine composition comprising just any polypeptide self-antigen or a scFv of a B-cell lymphoma surface immunoglobulin, wherein the polypeptide self-antigen or the scFv of a B-cell lymphoma surface immunoglobulin antigen express just any epitope or a tumor-specific vaccine in a subject at risk of developing a tumor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The nature of the invention: The claims of the instant invention are broadly drawn to a method of inducing a tumor-specific immune antibody response in a subject who has or had a tumor comprising administering any polypeptide self-antigen that is useful as a vaccine to treat any tumor, wherein the polypeptide is any epitope expressed on a tumor, and the polypeptide is produced by a cell or organism that has been transformed with a nucleotide sequence derived from a tumor of a subject (claim 41).

The state of the prior art and the predictability or lack thereof in the art:

The art teaches that B-cell lymphomas express Ig molecules on the surface of the cell. These Ig molecules can be utilized as potential B-cell tumor markers, and as such, anti-idiotypic antibodies that are either whole antibodies or antibody fragments that recognize idiotypes on the surface expressed Ig molecules can used as an antigen, eliciting the immune response against the B-cells expressing such Ig molecules on their surfaces (see Caspar et al (Blood 1997; 90(9):3699-3706) and McCormick et al (PNAS USA 1999;96:703-708)). The art also teaches that products, that are intended as cancer vaccines, are challenging and perhaps impossible wherein the "notion that cancer vaccines will replace standard therapeutic strategies in malignant disease still belongs to the realm of fiction." (Evans et al, Q J Med, 92:299-307, 1999, see page 303). According to Donnelly J. (Nature Medicine, 11(9): 1354-1356, Nov. 2003) "treating cancer with something that looks more like a modern-day vaccine, with a defined antigen and an optimized adjuvant and delivery platform, is still in the future" (see page 1354 lines 13-17). Further, DeGruijl T. D. (Nature Medicine, 5(10):1124-1125, Oct. 1999) teach that a variety of anti-tumor vaccine trials have been undertaken and in spite of the large number of these trials, and the plethora of distinct approaches investigated, there has been little evidence of clinical efficacy. DeGruijl also states "precise correlates of clinical effects and immunological responses have been lacking" (see page 1124, left column). Thus, Applicant is not enabled for the instantly claimed method of using a vaccine composition.

The amount of direction or guidance present and the presence or absence of working examples: The instant specification has taught the isolation of polynucleotide sequences encoding VH and VL regions of a surface expressed Ig molecule from bone marrow aspirates by RT-PCR. The specification also discloses the generation of a polynucleotide sequence encoding an scFv to be used as an antigen to elicit a polyclonal antibody immune response for the treatment of B-cell lymphomas. The specification does not teach a method of inducing a tumor-specific immune antibody response in a subject that has or had a B cell lymphoma or at risk of developing a B cell lymphoma comprising administering to said subject any other polypeptide self antigens other than scFvs constructed from the VH and VL domains of immunoglobulins expressed on the surface of B cell lymphomas. Furthermore, the specification does not teach a method of inducing a tumor-specific immune antibody response in a subject that has or had just any tumor or at risk of developing just any tumor comprising administering to said subject a scFv of a B-cell lymphoma surface immunoglobulin. As a result, one of skill in the art would not be able to practice the invention commensurate in scope with the claims without undue experimentation. Again, the teachings in the specification are limited to a polynucleotide encoding a scFv, which is one type of epitope found on the surface of a specific type of tumor, namely, B-cell lymphomas. The specification has also not taught any vaccine or method of inducing a tumor-specific antibody immune response in a subject at risk of developing a tumor because it is difficult to determine the population that would be at risk of developing a tumor and the

skilled artisan would be forced into undue experimentation to determine the population that would be predisposed to developing just any tumor or even B cell lymphomas.

The breadth of the claims and the quantity of experimentation needed: Given the broad range of peptides, tumors and patient population encompassed within the claims, which includes any polypeptide self-antigen, any tumor type, including tumors that don't necessarily express the polypeptide self-antigen or a surface Ig, and patient populations that are at risk of developing a tumor, and absent sufficient teachings in the specification to overcome the teachings of unpredictability found in the art, it would require undue experimentation by one of ordinary skill in the art to be able to practice the invention commensurate in scope with the claims.

9. Claims 41-44, 46-50 and 54-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing a B cell lymphoma-specific immune antibody response in a subject who has or had a B cell lymphoma comprising administering a scFv of a B-cell lymphoma surface immunoglobulin antigen (i.e., idiotype), wherein the scFv comprises both VH and VL domains, wherein the VH and VL domains comprise 6 CDRs, three from the VH domain and three from the VL domain, does not reasonably provide enablement for a method of inducing a tumor-specific immune antibody response in a subject who has or had a B cell lymphoma comprising administering a scFv of a B-cell lymphoma surface immunoglobulin

antigen (i.e., idiotype), wherein the scFv only comprises part of the VH and part of the VL or less than the full-complement of CDRs from both the VH and VL chains as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method of inducing a tumor-specific immune antibody response in a subject who has or had a B cell lymphoma comprising administering a scFv of a B-cell lymphoma surface immunoglobulin antigen (i.e., idiotype), wherein the scFv only comprises part of the VH and part of the VL or less than the full-complement of CDRs from both the VH and VL chains. The claim language encompasses fragments of the VH and VL domains, which do not contain a full set of 6 CDRs and would not form idotypes, which are conformational-dependent epitopes.

The specification discloses that an idiotype or epitope thereof formed by the association of the CDRs of both the VH and VL domains. The specification does not enable an idiotype that is formed by the association of less than the full complement of CDRs from both the VH and VL domains or fragments of the VH and VL domains.

The claims encompass a method of inducing a tumor-specific immune antibody response in a subject who has or had a B cell lymphoma comprising administering a scFv of a B-cell lymphoma surface immunoglobulin antigen (i.e., idiotype), wherein the scFv only comprises part of the VH and part of the VL or less than the full-complement of CDRs from both the VH and VL chains. Benvenuti et al (Gene Therapy, 8(20):1555-1561, October 2001) teach that scFv DNA vaccination results in a highly specific anti-idiotypic immune response that strictly depends on the quaternary structure of the idiotype (see page 1559, right column). "The anti-idiotype immune response was directed exclusively at the original immunising VL/VH combination, with complete absence of antibodies recognizing determinants in any of the single V regions displayed in the context of a different idiotype." (Benvenuti et al, see page 1558). Thus, Benvenuti et al demonstrate that the parental V regions association is an absolute requirement to induce anti-idiotype antibodies and these antibodies are exclusively against conformational combined VL/VH determinants (see page 1557 and abstract). Thus, it is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences, which maintain their required conformation, are required in order to induce a B cell lymphoma-specific immune

antibody response that bind conformation dependent idiotypes expressed on B cell lymphomas (i.e., anti-idiotype antibodies). It is unlikely that an idiotype or an immunogenic composition or therapeutic composition comprising said idiotype, which comprises only part of the VH and part of the VL or less than the full-complement of CDRs from both the VH and VL chains as defined by the claims, have the required conformational combined VH/VL determinants or epitopes (i.e., idiotypes). Applicants have provided insufficient evidence or nexus that would lead the skilled artisan to predict the ability of using an idiotype for inducing a B cell lymphoma-specific immune antibody response in the treatment of B-cell lymphomas, wherein said idiotype comprises only part of the VH and part of the VL or less than the full-complement of CDRs from both the VH and VL chains. One of skill in the art would neither expect nor predict the appropriate functioning of the idiotype as broadly as is claimed.

Therefore, in view of the lack of guidance in the specification and in view of Benvenuti et al, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to a method of inducing a B cell lymphoma-specific immune antibody response in a subject who has or had B cell lymphoma comprising administering an idiotype useful in the treatment of B-cell lymphomas and an immunogenic composition or therapeutic composition comprising administering an idiotype that comprises only part of the VH and part of the VL or less than the full-complement of CDRs from both the VH and VL chain. Undue experimentation would be required to produce

the invention commensurate with the scope of the claims from the written disclosure alone.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 41-47 and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Casper et al (Blood, 90(9):3699-3706, November 1997).

The claims are drawn to a method of inducing a tumor-specific immune antibody response in a subject who has or had a tumor comprising administering to said subject a composition comprising a polypeptide self-antigen encoded by a nucleic acid in the cells of said tumor, wherein: (1) the epitope is unique to or over expressed by the tumor cells, (2) the polypeptide is produced in a cell or organism transformed by the nucleic acid, (3) the polypeptide is obtained from the transformed cell or organism in correctly folded form, and (4) the polypeptide self-antigen is capable of inducing an immune response and a pharmaceutically acceptable carrier or excipient. The polypeptide self-antigen is a single chain antibody that includes at least part of the VH and VL domains that are linked by an amino acid linker that has between one and about 50 residues, consists of

between one and twelve different amino acids and facilitates secretion and correct folding of the scFv to mimic the tumor epitope (surface Ig on B cell lymphomas) in its native form on the tumor cell. Further, the tumor is a B-cell lymphoma and administration is by a parenteral route, which is subcutaneous, transdermal or intramuscular route.

Casper et al teach a method of inducing a B cell lymphoma-specific immune antibody response in a subject comprising administering a scFv that includes the VH and VL domains (i.e., at least part of the VH and VL domains) connected by a flexible 16 amino acid linker $((Gly_3Ser_1)_4)$, wherein the VH and VL domains are from immunoglobulins expressed on B cell lymphomas (i.e., epitopes unique to the tumor cells) (see entire document). Casper et al teach the production of the scFv (idiotype) in a cell which was transformed by a nucleotide sequence that encoded the scFv, which was able to induce a cell mediated immune response (i.e., Th1) as well as polyclonal antibodies (see page 3701, right column and page 3704, right column and Figure 2). Because the scFv (idiotype) induced the production of polyclonal antibodies that are reactive with the surface immunoglobulin on B cell lymphomas, it is inherent that the linker facilitates secretion and correct folding of the scFv to mimic the native form of the immunoglobulin (i.e., tumor epitope) expressed on the surface of B cell lymphomas. Casper et al also teach that the scFv was injected subcutaneously (parenteral route) and it is inherent that the scFv was prepared in a pharmaceutically acceptable carrier or excipient to facilitate the in vivo administration of the scFv.

12. Claims 41-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Hawkins et al (WO 94/08008, 4/14/1994).

The claims have been described supra.

Hawkins et al teach a method of inducing a B cell lymphoma-specific immune antibody response in a subject comprising administering a scFv that includes the VH and VL domains (i.e., at least part of the VH and VL domains), wherein the VH and VL domains are from immunoglobulins expressed on B cell lymphomas (i.e., epitopes unique to the tumor cells) (see entire document, particularly pages 2-8 and 19-20). Thus, the scFv includes an epitope that is unique to B cell lymphoma cells, includes the VH and VL domains, which are at least part of the VH and part of the VL, respectively. Hawkins et al teach the scFv in PBS (i.e., a pharmaceutically acceptable carrier or excipient) administered to subject by subcutaneous immunization (parenteral route) at 12.5 μg three times about two weeks apart (see page 19). Hawkins et al teach that administration of the scFv generated a polyclonal anti-idiotypic antibody response, which was detected by testing the sera of the host by ELISA (enzyme immunoassay) and flow cytometry (FACS analysis) (see pages 7 and 20-21).

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 41-50 and 54-57 are rejected under 35 U.S.C.103(a) as being unpatentable over Caspar et al (Blood, 90(9):3699-3706, November 1997) in view of Tang et al (Journal of Biological Chemistry, 271(26):15682-15686, June 1996) and Hsu et al (Blood, 89(9):3129-3135, 1 May 1997).

Claims 41-47 and 54 have been described supra.

Claims 48-50 further limit the method of inducing a tumor-specific immune response in a subject by reciting that the polypeptide self antigen is in unit dose form in aqueous solution at a concentration between about 0.1 and about 10 mg/ml and the subject is a human. Claims 55-57 further limit the linker of claim 54 by reciting that the linker is a member of a randomized library of linkers with the following requirements: position 1 cannot be the same nucleotide as position 2 of a repeated triplet, position 2 cannot be the same nucleotide as position 3 of a repeated triplet, and position 1 cannot be the same nucleotide as position 3 of a repeated triplet (claim 55), wherein the nucleotide in the first and second positions of each repeated triplet is selected from any two of dA, dG, dC or dT (claim 56) and wherein the linker at position 1 is dA or dG, position 2 is dC or dG, and position 3 is dT (claim 57).

Caspar et al have been described supra. Casper et al also teach that patients who initially responded to anti-Idiotype monoclonal antibody eventually relapsed with a tumor that did not bind the monoclonal antibody used for the treatment due to mutations in the immunoglobulins expressed by tumor cells and that the polyclonal immune response evoked by active immunization with tumor idiotypes can cover bona fide tumor variants that escaped treatment in a patient

during therapy with an anti-Idiotype monoclonal antibody (see page 3699, left column and page 3705). Caspar et al does not specifically teach the scFv in unit dosage form in aqueous solution at a concentration between about 0.1 and 10 mg/ml or administration to a human subject or a randomized library of linkers with the instantly claimed criteria. These deficiencies are made up for in the teachings of Tang et al and Hsu et al.

Tang et al teach that a linker suitable for one scFv will not be optimal for other scFvs and linker length and sequence affect the expression level, solubility, stability and binding affinity of the scFvs (see page 15682, right column). Tang et al teach a method of selecting active scFvs synthesized form libraries of scFv genes with randomized linker DNA sequences (see abstract and pages 15682-15684).

Hsu et al teach clinical trials in which patients with B cell lymphoma receiving subcutaneous immunization of 0.5 mg of B cell lymphoma immunoglobulin induced specific immune responses (humoral) against the immunoglobulin (anti-idiotype immune responses) expressed by their own B cell lymphomas and the ability to make such an immune response is correlated with a more favorable clinical outcome (see abstract, page 3130, right column, page 3131, right column). Hsu et al teach "The FFP [freedom from disease progression] and survival of those patients mounting an antitumor Id immune response is significantly longer compared to those who did not develop an immune response or to that of nonvaccinated, historical controls".

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method of inducing a B cell lymphoma-specific antibody response in a human subject against the idiotype expressed on their own B cell lymphomas by administering a scFv comprising the VH and VL domains from the Ig expressed on B cell lymphomas (tumor idiotype), wherein the VH and VL domains are connected by a randomized linker for therapeutic benefit of B cell lymphomas.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method of inducing a B cell lymphoma-specific antibody response in a human subject against the idiotype expressed on their own B cell lymphomas by administering a scFv comprising the VH and VL domains from the Ig expressed on B cell lymphomas (tumor idiotype), wherein the VH and VL domains are connected by a randomized linker for therapeutic benefit of B cell lymphomas in view of Caspar et al and Tang et al and Hsu et al because Caspar et al teach a method of inducing a B cell lymphoma-specific immune antibody response in a subject comprising administering a scFv that includes the VH and VL domains from immunoglobulins expressed on B cell lymphomas and Tang et al teach that a linker suitable for one scFv will not be optimal for other scFvs and linker length and sequence affect the expression level, solubility, stability and binding affinity of the scFvs and Tang teaches a method of selecting functional scFvs synthesized form libraries of scFv genes with randomized linker DNA sequences. Therefore, it would have been obvious to one skilled in the art at the time the

invention was made to have selected functional scFvs having randomized linker DNA sequences in order to optimize the expression level, solubility, stability and binding affinity of the scFvs as taught by Tang et al and to have used optimized scFvs in the method of Caspar et al for therapeutic benefit of B cell lymphomas. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a method of inducing a B cell lymphoma-specific antibody response in a human subject against the idiotype expressed on their own B cell lymphomas by administering a scFv comprising the VH and VL domains from the Ig expressed on B cell lymphomas (tumor idiotype), wherein the VH and VL domains are connected by a randomized linker for therapeutic benefit of B cell lymphomas in view of Caspar et al and Tang et al and Hsu et al because Hsu et al teach clinical trials in which patients with B cell lymphoma receiving subcutaneous immunization of 0.5 mg of B cell lymphoma immunoglobulin induced specific immune responses against the immunoglobulin (anti-idiotype immune response) expressed by their own B cell lymphomas and the ability to make such an immune response is correlated with a more favorable clinical outcome. Furthermore, it would have been obvious at the time the invention was made to have immunized a B cell lymphoma patient with the scFv as taught by for inducing a polyclonal antibody response that is capable of recognizing multiple antigenic determinants and, therefore, may prevent escape of tumor cells with mutations in their idiotypes as taught by Caspar et (see page 3699, bridging paragraph of left and right columns) and Hsu et al (see page 3129,

bridging paragraph of left and right columns). Thus, it would have been obvious to one skilled in the art at the time the invention was made to have produced a method of inducing a B cell lymphoma-specific antibody response in a human subject against the idiotype expressed on their own B cell lymphomas by administering a scFv comprising the VH and VL domains from the Ig expressed on B cell lymphomas (tumor idiotype), wherein the VH and VL domains are connected by a randomized linker for therapeutic benefit of B cell lymphomas in view of Caspar et al and Tang et al and Hsu et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

15. Claims 41-50 and 54-57 are rejected under 35 U.S.C.103(a) as being unpatentable over Hawkins et al (WO 94/08008, 4/14/1994) in view of Tang et al (Journal of Biological Chemistry, 271(26):15682-15686, June 1996) and Hsu et al (Blood, 89(9):3129-3135, 1 May 1997).

The claims have been described supra.

Hawkins et al have been described supra. Hawkins et al does not specifically teach the scFv in unit dosage form in aqueous solution at a concentration between about 0.1 and 10 mg/ml or administration to a human subject or an amino acid linker that has between one and about 50 residues, consists of between one and twelve different amino acids and facilitates secretion and correct folding of the scFv to mimic the tumor epitope in its native

form on the tumor cells or a randomized library of linkers with the instantly claimed criteria. These deficiencies are made up for in the teachings of Tang et al and Hsu et al

Tang et al have been described supra.

Hsu et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method of inducing a B cell lymphoma-specific antibody response in a human subject against the idiotype expressed on their own B cell lymphomas by administering a scFv comprising the VH and VL domains from the Ig expressed on B cell lymphomas (tumor idiotype), wherein the VH and VL domains are connected by a randomized linker for therapeutic benefit of B cell lymphomas.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method of inducing a B cell lymphoma-specific antibody response in a human subject against the idiotype expressed on their own B cell lymphomas by administering a scFv comprising the VH and VL domains from the Ig expressed on B cell lymphomas (tumor idiotype), wherein the VH and VL domains are connected by a randomized linker for therapeutic benefit of B cell lymphomas in view of Hawkins et al and Tang et al and Hsu et al because Hawkins et al teach a method of inducing a B cell lymphoma-specific immune antibody response in a subject comprising administering a scFv that includes the VH and VL domains from immunoglobulins expressed on B cell lymphomas and Tang et al teach that a

linker suitable for one scFv will not be optimal for other scFvs and linker length and sequence affect the expression level, solubility, stability and binding affinity of the scFvs and Tang teaches a method of selecting functional scFvs synthesized form libraries of scFv genes with randomized linker DNA sequences. Therefore, it would have been obvious to one skilled in the art at the time the invention was made to have selected functional scFvs having randomized linker DNA sequences in order to optimize the expression level, solubility, stability and binding affinity of the scFvs as taught by Tang et al and to have used optimized scFvs in the method of Hawkins et al for therapeutic benefit of B cell lymphomas. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a method of inducing a B cell lymphoma-specific antibody response in a human subject against the idiotype expressed on their own B cell lymphomas by administering a scFv comprising the VH and VL domains from the Ig expressed on B cell lymphomas (tumor idiotype), wherein the VH and VL domains are connected by a randomized linker for therapeutic benefit of B cell lymphomas in view of Hawkins et al and Tang et al and Hsu et al because Hsu et al teach clinical trials in which patients with B cell lymphoma receiving subcutaneous immunization of 0.5 mg of B cell lymphoma immunoglobulin induced specific immune responses against the immunoglobulin (anti-idiotype immune response) expressed by their own B cell lymphomas and the ability to make such an immune response is correlated with a more favorable clinical outcome. Furthermore, it would have been obvious at the time the invention was

made to have immunized a B cell lymphoma patient with the scFv as taught by for inducing a polyclonal antibody response that is capable of recognizing multiple antigenic determinants and, therefore, may prevent escape of tumor cells with mutations in their idiotypes as taught by Hawkins et (see page 7, lines 7-10) and Hsu et al (see page 3129, bridging paragraph of left and right columns). Thus, it would have been obvious to one skilled in the art at the time the invention was made to have produced a method of inducing a B cell lymphoma-specific antibody response in a human subject against the idiotype expressed on their own B cell lymphomas by administering a scFv comprising the VH and VL domains from the Ig expressed on B cell lymphomas (tumor idiotype), wherein the VH and VL domains are connected by a randomized linker for therapeutic benefit of B cell lymphomas in view of Hawkins et al and Tang et al and Hsu et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164

USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 41-50 and 54-57 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 41-50 of copending Application No. 10/067,790 in view of Tang et al (The Journal of Biological Chemistry, 271(26):15682-15686, 1996). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims are drawn to a method of inducing a tumor-specific immune antibody response in a human who has or had a tumor comprising administering to said human a composition comprising a polypeptide self-antigen in unit dosage form at a concentration between 0.1 and about 10 mg/ml, wherein the polypeptide self-antigen is encoded by a nucleic acid in the cells of said tumor, wherein: (1) the epitope is unique to or over expressed by the tumor cells, (2) the polypeptide is produced in a cell or organism transformed by the nucleic acid, (3) the polypeptide is obtained from the transformed cell or organism in correctly folded form, and (4) the polypeptide self-antigen is capable of inducing an immune response and a pharmaceutically acceptable carrier or excipient. The polypeptide self-antigen is a single chain antibody that includes at least part

of the VH and VL domains that are linked by an amino acid linker that has between one and about 50 residues, consists of between one and twelve different amino acids and facilitates secretion and correct folding of the scFv to mimic the tumor epitope (surface Ig on B cell lymphomas) in its native form on the tumor cell or the linker is a member of a randomized library of lnkers with the following requirements: position 1 cannot be the same nucleotide as position 2 of a repeated triplet, position 2 cannot be the same nucleotide as position 3 of a repeated triplet, and position 1 cannot be the same nucleotide as position 3 of a repeated triplet (claim 55), wherein the nucleotide in the first and second positions of each repeated triplet is selected from any two of dA, dG, dC or dT (claim 56) and wherein the linker at position 1 is dA or dG, position 2 is dC or dG, and position 3 is dT (claim 57). Further, the claims recite wherein the tumor is a B-cell lymphoma and administration is by a parenteral route, which is subcutaneous, transdermal or intramuscular route.

Application No. 10/067,790 The instant claims are drawn to a method of inducing a tumor-specific immune antibody response in a human who has or had a tumor comprising administering to said human a composition comprising a polypeptide self-antigen in unit dosage form at a concentration between 0.1 and about 10 mg/ml, wherein the polypeptide self-antigen is encoded by a nucleic acid in the cells of said tumor, wherein: (1) the epitope is unique to or over expressed by the tumor cells, (2) the polypeptide is produced in a cell or organism transformed by the nucleic acid, (3) the polypeptide is obtained from the transformed cell or organism in correctly folded form, and (4) the polypeptide

self-antigen is capable of inducing an immune response and a pharmaceutically acceptable carrier or excipient. Further, the claims recite wherein the tumor is a B-cell lymphoma and administration is by a parenteral route, which is subcutaneous, transdermal or intramuscular route. The claims in 09/434,870 do not teach a single chain antibody that includes the VH and VL linked by an amino acid linker that has between one and about 50 residues, consists of between one and twelve different amino acids and facilitates secretion and correct folding of the scFv to mimic the tumor epitope (surface Ig on B cell lymphomas) in its native form on the tumor cell or a randomized library of linkers with the following requirements: position 1 cannot be the same nucleotide as position 2 of a repeated triplet, position 2 cannot be the same nucleotide as position 3 of a repeated triplet, and position 1 cannot be the same nucleotide as position 3 of a repeated triplet (claim 55), wherein the nucleotide in the first and second positions of each repeated triplet is selected from any two of dA, dG, dC or dT (claim 56) and wherein the linker at position 1 is dA or dG, position 2 is dC or dG, and position 3 is dT (claim 57). These deficiencies are made up for in the teachings of Tang et al.

Tang et al have been described supra.

The claims in the instant application are obvious variants of Application No. 10/067,790 because it would have been prima facie obvious to have selected functional scFvs having randomized linker DNA sequences in order to optimize the expression level, solubility, stability and binding affinity of the scFvs as taught by Tang et al for therapeutic benefit of B cell lymphomas.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have selected functional scFvs having randomized linker DNA sequences in order to optimize the expression level, solubility, stability and binding affinity of the scFvs as taught by Tang et al for therapeutic benefit of B cell lymphomas because Tang et al teach that a linker suitable for one scFv will not be optimal for other scFvs and linker length and sequence affect the expression level, solubility, stability and binding affinity of the scFvs and Tang teaches a method of selecting functional scFvs synthesized form libraries of scFv genes with randomized linker DNA sequences.

This is a provisional obviousness-type double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
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PRIMARY EXAMINER